Intravenous antiplatelet agents such as IIb/IIIa inhibitors or cangrelor may offer a bridge for this initial delay of antiplatelet action of ticagrelor administered as either a standard or double LD. Alternatively, earlier (i.e., pre-hospital) administration of ticagrelor may lead to better platelet inhibition during primary PCI. The clinical utility of this strategy is being tested by the ongoing ATLANTIC study (NCT01347580).

Our study was not randomized; however, demographic and clinical characteristics were balanced between patients treated with a double and a standard LD. Furthermore, a propensity score was used to adjust for potential biases. The study was purely pharmacodynamic, not allowing any conclusions on clinical outcome. We used only 1 method for platelet function testing; however, VerifyNow is the most validated method and correlates well with light transmittance aggregometry. The lack of pharmacokinetic data does not allow elucidation of the exact mechanisms responsible for the double LD delayed onset of action of ticagrelor. In this small study, a double LD was well tolerated, which is consistent with a previous report (5).

In patients with STEMI undergoing primary PCI, doubling the LD of ticagrelor is not accompanied by a faster than standard dose onset of antiplatelet action.

***Dimitrios Alexopoulos, MD†**
Vassilios Gkizas, MD†
Sotirios Patsilinakos, MD‡
Ioanna Xanthopoulou, MD†
Christos Angelidis, MD§
Prodromos Anthopoulos, MD‖
George Makris, MD†
Angelos Perperis, MD†
Stavros Karanikas, MD‡
Nikolaos Koutsogiannis, MD†
Periklis Davlouros, MD†
Spyridon Deftereos, MD§
John Chiladakis, MD†
George Hahalis, MD†

*Department of Cardiology, Patras University Hospital, Rion 26500, Patras, Greece
E-mail: dalex@med.upatras.gr

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From the †Department of Cardiology, Patras University Hospital, Rion, Patras, Greece; ‡Department of Cardiology, Konstantopoulio General Hospital, Athens, Greece; §Department of Cardiology, Athens General Hospital "G. Gennimatas", Athens, Greece; and the ‖Catheterization Laboratory, Evangelismos Hospital, Athens, Greece.

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APPENDIX

For supplementary tables, please see the online version of this article.

Letters to the Editor

Troponin Testing for Detection of Acute Myocardial Infarction in Skeletal Muscle Disease Patients

Follow the Guidelines

In a recent letter to the editor of the *Journal* (1), Rittoo describes what he calls a "fundamental error" in the guidance documents on the diagnosis of acute myocardial infarction (AMI), namely, in the universal definition of AMI (2) and the expert consensus (3), with potential implications for the detection of AMI during increased skeletal muscle repair or disease events. In particular, Rittoo infers from 3 references (4–6), with overlapping authorship, that diseased skeletal muscle may re-express cardiac troponin T (cTnT), but not cTnI, which may then lead to elevated cTnT in serum. The author further states that the guidance documents wrongly define elevations of the marker in the circulation as "virtually diagnostic of myocardial necrosis."

In our view, Rittoo's statements were incorrect and misleading for several reasons. First, the suspected cardiac (un)specificity of cTnT could not be derived from the cited references (4–6). For example, the first study (4) compared different cTnT antibody generations and concluded that "circulating cTnT or cTnI in either end-stage renal disease (ESRD) or Duchenne muscular dystrophy (DMD) patients originates from the heart" (and not from skeletal muscle), which was in contrast to Rittoo's interpretation of these data. In the second cited reference (5), the bands in the Western blot analyses of DMD had a smaller molecular weight (molecular mass 33 to 39 kDa) compared with that from heart muscle or purified protein, suggesting that different cTnT isoforms were observed; importantly, it was found that the Roche antibody M7 was not reactive to these smaller cTnT isoforms (7). The different antibody reactivity therefore illustrates the utmost importance of including more than 1 antibody for both cTnT and cTnI isoforms when drawing general conclusions on their cardiac specificity and

eventual smaller fetal or degraded isoforms. It was therefore rather speculative to use the observations with non-Roche antibodies (5) to conclude that Roche's troponin assays were incorrect, as was done by Rittoo (1). The third reference (6) did not compare cTnI in diseased skeletal muscle with cTnT, so those comparative conclusions also appeared speculative (1).

Furthermore, using former antibody generations, the detection sensitivity for the different cTn isoforms differed up to 100-fold, also because of different degradation kinetics and complexation of the isoforms (8–10). A simplified differentiation between cTnT and cTnI, such as suggested by Rittoo (1), would thus not address the reported variability of different cTnI antibodies (11). Also, when using highly sensitive techniques, such as polymerase chain reaction (PCR), it could not be excluded that RNA in peripheral blood might contribute to positive PCR results in tissue analysis (12,13). Moreover, the references in Rittoo's letter were not representative because a more systematic literature search revealed that not only cTnT, but also cTnI and mRNA for cTnI, were found to be elevated in diseased skeletal muscle tissue (14,15) and in serum (16–21) of skeletal muscle disease patients. Therefore, Rittoo's conclusion that "chronic injury to skeletal muscle causes the release of cTnT but not cTnI" was not sufficiently supported by data. Neither cTnT nor cTnI was consistently found to be elevated in regenerating skeletal muscle (22), so that the source for the occasionally detected cTn isoforms in diseased skeletal muscle was unclear in general. In other words, there was no sufficient evidence that 1 of the 2 addressed troponin isoforms would be more or less cardiac specific than the other. Additionally, it also seemed that the absence of other troponin relevant comorbidities was not adequately ruled out (4–6).

A similarly controversial discussion started in the 1990s on elevated serum troponin in ESRD when an improved assay sensitivity and considerations on different standardizations helped to clarify that elevated serum cTnT was correlated with risk for cardiac disease and morbidity (23,24), which then became a helpful predictor of mortality in hemodialysis patients as proposed by clinical guidelines (25). Thus, the question of clinical relevancy is whether a troponin elevation in skeletal muscle disease patients may be of similar prognostic relevance in ESRD patients. Accordingly, patients with skeletal muscular dystrophy are at increased risk of cardiac disease (26).

Second, and most importantly, the guidance documents were not properly applied in Rittoo's letter. The guidelines clearly require additional elements for the diagnosis of AMI beyond a single elevation of troponin in the circulation. Specifically, the guidance documents deliberately require a rise and/or fall of serial troponin, such as evidenced by a repeated troponin measurement. To date, such a rise and/or fall has not been documented in skeletal muscle disease patients in the absence of an AMI. This makes the troponin T assay clinically useful to detect AMI in patients, disregarding the eventual presence of rare skeletal muscle diseases.

Similarly, Rittoo's "fundamental error" accusation toward the guideline writing committees lacks an adequate scientific basis and a proper interpretation of the guidelines. Again, both guidance documents (2,3) do not propose a single troponin elevation per se as being indicative for AMI, but instead, a troponin rise and/or fall and clinical evidence of myocardial ischemia (e.g., symptoms, electrocardiographic changes, or imaging evidence) (3). These criteria ensure the fundamental differentiation between acute elevations of troponin in cases of AMI and chronically elevated troponin levels in other diseases (27).

In conclusion, it is our view that: 1) the cTnT assay is suited to support the diagnosis of AMI in patients with or without skeletal muscle disease; and 2) neither the American College of Cardiology Foundation nor other organizations will need to amend their recommendations.

***André Ziegler, PhD**
Sylvie Menassanch-Volker, PhD
Christian Zaugg, PhD

*Roche Diagnostics International Ltd.
Forrenstrasse 2
CH-6343 Rotkreuz
Switzerland
E-mail: andre.ziegler@roche.com

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Is the Instantaneous Wave-Free Ratio Equivalent to Fractional Flow Reserve?

We read the paper by Sen et al. (1) with great interest; the study was designed to explore whether the instantaneous wave-free ratio (iFR) was an adenosine-free alternative to fractional flow reserve (FFR) for the assessment of coronary stenosis. Hyperemic stenosis resistance (HSR) was used as a reference standard to determine when iFR and FFR disagreed as to which index was most representative of the hemodynamic significance of the stenosis. It was concluded that iFR and FFR had equivalent agreement with classification of coronary stenosis severity by HSR, and the administration of adenosine did not improve diagnostic categorization. However, we have several concerns regarding the data the study presented.

First, the well-designed study only investigated 51 vessels, which significantly reduces the reliability of the result. We noticed that in the 4 lesions of 2 groups (iFR[−] and FFR(+); iFR(+) and FFR[−]), in which there was disagreement, HSR agreed with FFR in 1 case (50%) and with iFR in the other case (50%) for each group, respectively (1). Based on these data, how could we trust that iFR and FFR were equally representative of the hemodynamic significance of the stenosis rather than an element of serendipity? It was not convincible that "the proportion (7.7%) is consistent with clinical populations, the ADVISE Registry (6%), and South Korean Study (6%), suggesting that the study findings are consistent with other, larger datasets" (1).

Second, we noted that "using the established ischemic cut-off point of >0.8 mm Hg/cm·s for HSR (2)," a 0.75 cutoff point for FFR was found to have an optimal diagnostic efficiency of 0.96 (1). The cutoff for HSR was certainly key to the study, which was used to determine the cutoff of iFR and FFR and dominated the disagreement between them. However, the problem is that there is no evidence of the so-called "established ischemic cut-off point of >0.8 mm Hg/cm·s for HSR" in the study by Christou et al (2). What is wrong with that? Could we just explain it as a mistake? Because we did find a paper (3) to validate a cutoff of >0.8 mm Hg/cm·s for HSR, which was also cited in the study. If so, we have to know if this was the only paper (3) to date to determine such a cutoff of HSR without reproducibility. Furthermore, possible influences of hemodynamic alterations (heart rate, aortic pressure, contractility) on HSR have not been investigated (3).

In summary, it was of great significance for the study to clarify whether iFR was an adenosine-free alternative to FFR, especially when the VERIFY (Verification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in Everyday Practice) study (4) indicated that iFR correlates weakly with FFR and was not independent of hyperemia. However, maybe we should not take the urgency, but the large-sized algorithm, to clarify the issue. Moreover, it might be advisable to find a well-validated, pressure-and-flow index as a reference standard.

Guo-Xin Fan, MD
***Ya-Wei Xu, MD, PhD**

*Cardiology Department
Shanghai Tenth People's Hospital
Tongji University School of Medicine
301 Yanchang Road
Shanghai 200072
China
E-mail: xuyaweicn@yahoo.com.cn

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Reply

Is the Instantaneous Wave-Free Ratio Equivalent to Fractional Flow Reserve?

We are honored that Drs. Fan and Xu noticed some differences between the CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study) (1) and VERIFY